Phase 1 study of CA-170, a first-in-class, orally available, small molecule immune checkpoint inhibitor (ICI) dually targeting VISTA and PDL1, in patients with advanced solid tumors or lymphomas

Yung Jue Bang (Seoul National University Hospital), Jeffrey Sosman (Northwestern), Adil Daud (UCSF), Funda Meric-Bernstam (MDACC), Javier Garcia-Corbacho (Hospital Clinic i Provincial), Manish Patel (Florida Cancer Specialists/Sarah Cannon Research Institute), James Lee (UPMC), Kyu-Pyo Kim (Asan Medical Center), Joshua Brody (Mt. Sinai), Sun Young Rha (Yonsei University Health System - Severance Hospital), Marta Gil Martín (Catalan Institute of Oncology) , Santiago Ponce Aix (Hospital Universitario 12 de Octubre), Erika Hamilton (Sarah Cannon Research Insitute/Tennessee Oncology), Radhakrishnan Ramchandren (Karmanos), Myung-Ju Ahn (Samsung Medical Center), James Spicer (King's College London, Guy's Hospital), Simon Pacey (University of Cambridge & Cambridge University Hospitals NHS Foundation Trust), Gerald Falchook (SCRI Denver), Hongwei Wang, Guangxin Xu, Lisa Adams, Anna Wai See Ma, Robert Gharavi, P. Taylor Eves, David Tuck, John Powderly (Carolina BioOncology Institute)

Introduction

V-domain Ig suppressor of T-cell activation (VISTA) and Programmed-death 1 (PD-1) are independent immune checkpoints that negatively regulate T-cell function[1]. VISTA is expressed on both immune cells and tumor cells[2,3,4,5,6]. Most noticeably, strong expression of VISTA in epithelioid mesothelioma, strikingly higher than in other solid tumors, has implications for the immune response in this cancer with inhibitors blocking VISTA.[2] Furthermore, VISTA is found to be upregulated in cancers as a potential resistance mechanism after therapy with immune checkpoint inhibitors (ICI)[7,8]. As such it has been considered a target for ICI therapy. Pre-clinical studies demonstrated that dual blockade of both VISTA and PD-L1 can be synergistic[1]. CA-170 is a first-in-class small molecule oral inhibitor that directly targets VISTA and PDL1/L2 and has demonstrated anti-tumor activity in multiple preclinical models. This presentation is an update to the on-going Phase 1 trial (*Clinicaltrials.org* NCT02812875) presented last year[9]. A phase 2 study is also ongoing[10].

Methods and Study Design

CA-170 Phase 1 First-in-Human Dose Escalation Trial (CA-170-101)

- Accelerated titration of initial 3 cohorts, followed by a 3+3 design
- Selected dose levels back-filled with additional patients

Objectives

- *Primary*: Safety, Recommended Phase 2 Dose (RP2D), and MTD;
- *Secondary*: PK and anti-cancer activity
- *Exploratory*: biomarkers and PD effects

Patient Population

- Patients with advanced solid tumors or lymphoma for which standard therapy, does not exist, is not available, or is no longer effective.
- Eligible patients were aged ≥18 years with advanced solid tumors or lymphomas, adequate organ function, and ECOG PS 0–1.
- Study sites in South Korea, US, Spain, UK

Treatment

- Oral, QD or BID, dosing in continuous 21-day cycles

Baseline Patient Characteristics	n (%)
Male	34 (58)
Female	25 (42)
Age, median (range)	62 (26-86)
Weight [kg], median (range)	70 (44-117)
ECOG PS 0	11
ECOG PS 1	48
# of prior lines, median (range)	3 (0-9)

Dose Level	Total daily dose	Number of pts
50 mg QD	50 mg	1
100 mg QD	100 mg	1
200 mg QD	200 mg	1
400 mg QD	400 mg	12
600 mg QD	600 mg	17
800 mg QD	800 mg	14
600 mg BID	1200 mg	4
900 mg BID	1800 mg	5
1200 mg BID	2400 mg	4
	Total # of pts treated:	59

Baseline Disease Characteristics

Group 1

ICI therapy-naïve patients with tumor types approved for ICI. Positive PD-L1 status was not required per protocol. Based on prior testing, 9 out of 34 patients had positive PD-L1 status at baseline.

- *Median # of prior therapy = 3 (Range, 1-7)*

Group 2

ICI-naïve patients with tumor types without ICI approval

Group 3

Patients with prior exposure to at least one line of ICI therapy

Tumor type	Group 1 n	Group 2 n	Group 3 n	Total n (%)
Non small cell lung cancer	12	0	1	13 (22.0)
Colorectal	2[a]	7[b]	1[b]	10 (17)
SCCHN	8[d]	0	0	8 (13.6)
Ovary	0	4	1	5 (8.5)
Melanoma	4	0	0	4 (6.8)
Renal cell carcinoma	3	0	0	3 (5.1)
Breast	0	2	0	2 (3.4)
Oesophagus	0	1	1	2 (3.4)
Hodgkin's Lymphoma	2	0	0	2 (3.4)
Non-Hodgkin's Lymphoma	0	2	0	2 (3.4)
Other[c]	3	3	2	8 (13.6)
Total	34	19	6	59 (100)

a. MSI-H CRC
b. Three patients with MSS CRC [2 in Group 2; 1 in Group 3]
c. One each of the following in each group: Group 1 [MSI-H endometrioid, hepatocellular carcinoma, Merkel cell carcinoma], group 2 [lacrimal gland, gall bladder, pancreatic], group 3 [epididymal, anal].
d. Includes one pt recorded in the clinical database as "oral cavity"

Results: Overall Safety Summary

- No DLTs observed to date; MTD and RP2D have not yet been established.
- The majority of TEAEs and TRAEs have been mild/moderate (Gr. 1/2) and self-limiting or resolved with concomitant meds
- 33 SAEs have been reported among 20 pts. 2 SAEs were reported to be possibly related to study treatment (3.4%)
  - Gr. 3 vomiting in cycle 1 in a pancreatic cancer patient with upper GI tumor involvement and disease progression at the time of event
  - Gr. 3 elevated pancreatic enzyme (lipase) towards the end of Cycle 4 in a leiomyosarcoma patient treated at 800 mg QD; not associated with symptoms or evidence of inflammation per abdominal CT; patient discontinued due to disease progression at the time of this event
- 6 patients (12%) have discontinued study treatment due to adverse events unrelated to study drug. No discontinuation or dose reduction due to adverse reaction related to CA170.

Most Frequent TEAEs in ≥10% of Patients by Preferred Term	Total, N=59 n (%)
Any Treatment-Emergent AE	54 (91.5)
Fatigue	17 (28.8)
Nausea	16 (27.1)
Decreased appetite	13 (22.0)
Vomiting	12 (20.3)
Anemia	12 (20.3)
Constipation	10 (16.9)
Cough	9 (15.3)
Headache	8 (13.6)
Pyrexia	7 (11.9)

Most Frequent Grade ≥ 3 TEAEs in >1 Patient, by Preferred Term *	Total, N=59 n (%)
Any Grade 3 or Higher TE AE	26 (44.1)
Lipase increased	3 (5.1)
Pain	2 (3.4)
Anemia	2 (3.4)
Urinary tract infection	2 (3.4)
Syncope	2 (3.4)

Most Frequent TRAEs in >3 Patients by Preferred Term *	Total, N=59 n (%)
Any Treatment-Related AE	36 (61.0)
Fatigue	12 (20.3)
Nausea	9 (15.3)
Chills	5 (8.5)
Pruritus	5 (8.5)
Constipation	4 (6.8)
Vomiting	4 (6.8)
Pyrexia	4 (6.8)
Decreased appetite	4 (6.8)

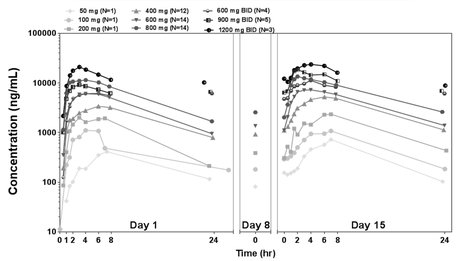
*A total of 5 patients experienced treatment-related adverse events (TRAEs) that were ≥Grade 3: 2 patients had lipase increased; 1 pat each of the following: amylase increased, blood bilirubin increased, fatigue, hypokalemia, nausea and vomiting.

- Two events of death were reported during study follow-up after the patients discontinued study treatment. In both cases, the death events were assessed by the investigators to be caused by disease progression and not related to CA-170

Pharmacokinetics

- Systemic exposures (C_{max}, C_{min}, C_{avg} and AUC) increased approximately proportionally with increasing doses for both QD and BID schedules.
- Comparing exposure of 600 mg QD to 600 mg BID at steady state, Cmax, Cmin and AUC/day of BID was 1.6 times, 5 times and twice of BID, respectively, suggesting significantly increased trough concentration with more frequent dosing.
- Inter-patient variability is within the expected range, given the potential impacting variables of oral administration, daily dosing and a highly heterogeneous patient population enrolled thus far.

CA-170 Plasma Concentration vs Time PK Profile



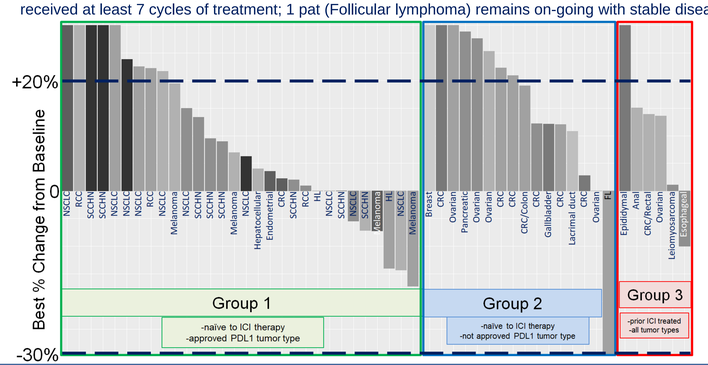
PK Parameters	Human Multi-Dose PK on C1D15 for QD and BID Dosing								
	50 mg QD (N=1)	100 mg QD (N=1)	200 mg QD (N=1)	400 mg QD (N=12) Mean ± SD	600 mg QD (N=14) Mean ± SD	800 mg QD (N=14) Mean ± SD	600 mg BID (N=4) Mean ± SD	900 mg BID (N=4) Mean ± SD	1200 mg BID (N=3) Mean ± SD
T_{max}† (hr)	7	7	7	6 (2-8)	3 (1.9-8)	2.5 (1-8.3)	3.6† ± (1.5 - 4.6)	2.1† ±(1.4 - 6.0)	3.0† ±(1.5 - 6.0)
C_{max} (ng/mL)	725	1078	2337	5753 ± 1663	8129 ± 4309	15367 ± 5190	12293 ±3054	20470 ±6798	28541 ±6713
$AUC_{0\text{-}24\ hr}$ (ng*hr/mL)	9540	15781	33951	78267 ± 26555	103496 ± 60428	175070 ± 70995	192242±5011 5	288406±1010 39	398271±7625 3
$T_{1/2}$ (hr)	5.9	6.7	7.1	7.8 ± 2.7	7.0 ± 2.4	7.0 ± 2.1	8.9 ±2.5	6.1 ±1.7	4.2 ±0.8
C_{min}‡ (ng/mL)	124	285	314.7	858.9 ± 612.0	1420.5 ± 1629.6	2414.8 ± 1939.2	5376 ±1949	6432 ±944	9652 ±3874
C_{avg} (ng/mL)	396	658	1414.6	3261.1 ± 1106.5	4312.3 ± 2517.8	7294.6 ± 2958.1	8010 ±2088	12017 ±4210	16595 ±3177

Anti-Tumor Activity Summary

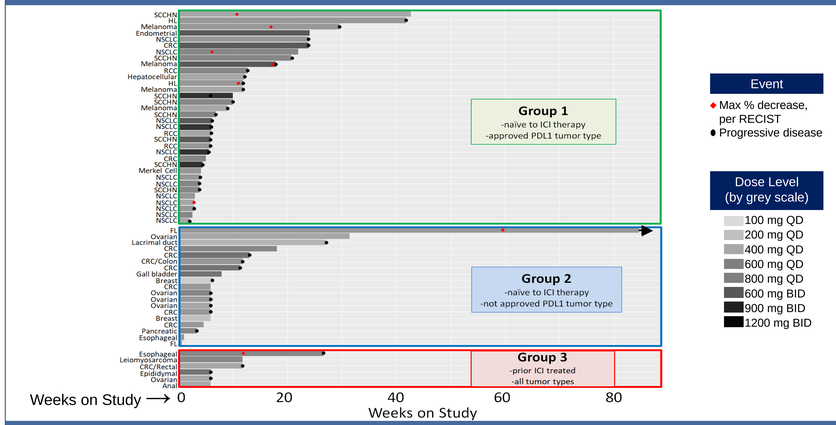
Group	Treated	Ongoing	Median (& range) weeks on treatment	Evaluable for Anti-tumor Activity	# of SD	Patients with Target Lesion Shrinkage
Total	59	1	6.1 (0.6 - 84.6)	50	25	8
Group 1	34	0	6.5 (2 - 42.7)	30	15	6
Group 2	19	1	5.9 (0.6 - 84.6)	14	7	1
Group 3	6	0	8.8 (5.9 - 26.6)	6	3	1

Anti-Tumor Activity Correlated with Tumor Types

- Overall, 50 patients were evaluable for anti-tumor activity with as least one post-baseline restaging.
- 25 pts (50%) showed SD per RECIST with 1 ongoing, 8 demonstrating tumor regression from baseline, 11 pts (19%) received at least 7 cycles of treatment; 1 pat (Follicular lymphoma) remains on-going with stable disease at >84 weeks.



Duration of Treatment



Conclusions and Future Directions

- The maximum dose is 1200mg BID, which is considered well tolerated.
- CA-170 has a favorable safety profile with preliminary evidence of anti-tumor activity (8 patients have experienced tumor regression from baseline).
- Signs of immune-modulating effect were also observed in peripheral blood and tumor tissue[11].
- CA-170, being the first small molecule oral inhibitor of immune checkpoints, demonstrates rapid absorption, good bioavailability, dose proportional PK and short half-life.
  - The short half-life allows the flexibility to control drug exposure and manage immune-related side effects.
  - Serious immune related events, reported with antibody ICIs, have been milder and reversible with the small molecule approach of CA-170 possibly due to quicker drug elimination after dose interruption.
  - CA-170 dose and dosing regimen are being optimized in relevant tumor types prior to initiation of confirmatory trials
- Clinical development of CA-170 is on-going with evaluation of potentially pharmacologically active BID dose in VISTA expressing tumors, including epithelioid mesothelioma which has strikingly higher VISTA expression than other solid tumors[2,3].
- Phase 2 study is ongoing in India conducted by our collaborator, Aurigene[10].

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Curis, Inc.
4 Maguire Road
Lexington, MA 02421
1-617-503-6500
www.curis.com

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